Chongxiang Chen¹²³*, Tianmeng Wen⁴*, Wei Liao¹²³

¹Department of Intensive Care Unit, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong Province, China; ²State Key Laboratory of Oncology in South China, Guangzhou 510060, Guangdong Province, China; ³Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, Guangdong Province, China; ⁴Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong Province, China. *Equal contributors.

Received December 4, 2018; Accepted April 10, 2019; Epub June 15, 2019; Published June 30, 2019

Abstract: Background: Asthma affects more than 315 million people worldwide, with approximately 10% having severe or uncontrolled asthma. This study is based on the dose regimens derived from the phase III randomized controlled trials (RCTs) to find out the most beneficial regimen of IL-5 monoclonal antibody to decrease annual rate of exacerbations in patients with severe asthma. Methods: PubMed and the Web of Science were used to find out the including studies. RevMan 5.1 and Stata 15.1 were performed to this systemic review and network meta-analysis. Results: After searching and screening articles, 9 articles about 10 studies with 5408 patients, and 6 arms with 3 major antibodies (mepolizumab, benralizumab, reslizumab) were included. Compared with placebo, the IL-5 monoclonal antibody group has lower annual rate of exacerbations. Ranking the regimens in the order of estimated probabilities of each treatment by using the network meta-analysis, the results show that reslizumab 3 mg/ kg was the best one (57.3%), followed by mepolizumab 100 mg SC (14.9%), mepolizumab 75 mg IV (14.3%), benralizumab 30 mg q8w (10.8%), benralizumab 30 mg q4w (2.7%), and placebo (0.0%). Reslizumab 3 mg/ kg was more efficacious than other therapeutic regimens. Conclusion: IL-5 monoclonal antibody can decrease the annual rate of exacerbations in asthma patients. Therefore, the regimen of reslizumab 3 mg/kg is probably the best choice to treat patients with severe asthma.

Keywords: Severe asthma, IL-5 monoclonal antibody, annual rate of exacerbation

Introduction

Asthma affects more than 315 million people all around the world, with about 10% of them having severe asthma [1, 2]. Patients with severe asthma need high-dosage inhaled corticosteroids in combination with long-acting β₂-agonists (LABA) to control their disease and they have considerable morbidity, characterized by frequent symptoms and exacerbations that often require coming to the Emergency Department and Hospital, but sometimes asthma remains “uncontrolled” despite this treatment [3].

Currently, some IL-5 monoclonal antibody agents (benralizumab, reslizumab, mepolizumab) have been approved by the Food and Drug Administration (FDA) to be used for treating severe asthma and these studies showed that they can help control the symptoms of severe asthma, as well as decrease the annual rate of clinically significant exacerbations, defined as worsening of asthma requiring systemic corticosteroids administered intravenously or orally for ≥3 days or as a single intra-muscular dose, or an emergency room visit or admission to hospital [4].

There have been two studies for conducting the meta-analysis to compare the advantages of these people. One of them compared the dose regimens of these agents containing phase I and II RCTs, and the other just compared resli-
zumab and benralizumab [5, 6]. The result of these studies showed that reslizumab was superior. However, the results in these studies above were not ideal because more phase III RCTs showed up recently. Therefore, network meta-analysis was performed here to determine whether IL-5 monoclonal antibody would be more appropriate for treating severe asthma in clinical practice.

Methods

Search strategy

Two investigators independently reviewed the identified abstracts and selected articles for full reviewing and the discrepancies were resolved by a third reviewer. The reference lists of eligible studies and relevant papers were also manually searched and reviewed. The search terms were “mepolizumab”, “benralizumab”, “reslizumab”, and “asthma” et al. The search date was until 2018/10/22. Finally 552 articles, excluding 251 duplications were found, which included 23 articles through reading the title and abstract, and 9 studies about 10 RCTs [4, 7-14] by reading the whole article (Figure 1).

Figure 1. Flow Diagram of choosing the appropriated articles.

Inclusion and exclusion

Inclusions contain: (1) research study focused on IL-5 antibody for treating severe asthma, (2)
## Table 1. Characteristics of studies included in the network meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Total number of patients</th>
<th>Number of annual exacerbation</th>
<th>RCT</th>
<th>One Center</th>
<th>Phase</th>
<th>Country</th>
<th>Age</th>
<th>Follow up</th>
<th>Precondition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basu 2017</td>
<td>Mep 75 IV/Mep 100 SC/Placebo</td>
<td>191/194/191</td>
<td>178/161/332</td>
<td>Yes</td>
<td>Multi</td>
<td>/</td>
<td>USA</td>
<td>Total: 12-82 years</td>
<td>40 w</td>
<td>≥2 asthma exacerbations; require high-dose ICS in the previous years</td>
</tr>
<tr>
<td>Bleecker 2017</td>
<td>Ben 30 Q4 w/Ben 30 Q8 w/Placebo</td>
<td>399/398/407</td>
<td>306/305/524</td>
<td>Yes</td>
<td>Multi</td>
<td>3</td>
<td>USA</td>
<td>Total: 12-75 years 50±14/51±14.5/49±14.3</td>
<td>48 w</td>
<td>Medium or high-dose ICS plus LABA treatment in the previous years</td>
</tr>
<tr>
<td>Chupp 2017</td>
<td>Mep 100 SC/Placebo</td>
<td>274/277</td>
<td>140/335</td>
<td>Yes</td>
<td>Multi</td>
<td>3 b</td>
<td>USA</td>
<td>Total: ≥12 years 49±14/52±14.9</td>
<td>24 w-L</td>
<td>≥2 asthma exacerbations; require high-dose ICS or others in the previous years</td>
</tr>
<tr>
<td>FitzGerald 2016</td>
<td>Ben 30 Q4 w/Ben 30 Q8 w/Placebo</td>
<td>357/364/370</td>
<td>235/249/379</td>
<td>Yes</td>
<td>Multi</td>
<td>3</td>
<td>USA</td>
<td>Total: 12-75 years 50±13.6/49±14.3/48±15.1</td>
<td>56 w</td>
<td>≥2 asthma exacerbations; require high-dose ICS in the previous years</td>
</tr>
<tr>
<td>Halder 2009</td>
<td>Mep 750 IV/Placebo</td>
<td>29/32</td>
<td>58/109</td>
<td>Yes</td>
<td>One</td>
<td>/</td>
<td>UK</td>
<td>Total: ≥18 years (21-63)/50 (24-72)</td>
<td>50 w</td>
<td>≥2 asthma exacerbations; require high-dose ICS in the previous years</td>
</tr>
<tr>
<td>Nair 2017</td>
<td>Ben 30 Q4 w/Ben 30 Q8 w/Placebo</td>
<td>72/73/75</td>
<td>60/39/137</td>
<td>Yes</td>
<td>Multi</td>
<td>/</td>
<td>Germany</td>
<td>Total: ≥18 years 50.2±12/52.9±10.1/49.9±11.7</td>
<td>28 w</td>
<td>Require oral glucocorticoids for 6 months or more</td>
</tr>
<tr>
<td>Castro 2015; study 1</td>
<td>Res/Placebo</td>
<td>245/245</td>
<td>221/441</td>
<td>Yes</td>
<td>Multi</td>
<td>3</td>
<td>USA</td>
<td>Total: 12-75 years 48 (38-57)/49 (38-57)</td>
<td>52 w</td>
<td>≥1 asthma exacerbations; Require high-dose ICS in the previous years</td>
</tr>
<tr>
<td>Bel 2014</td>
<td>Mep 100 SC/Placebo</td>
<td>69/66</td>
<td>99/140</td>
<td>Yes</td>
<td>Multi</td>
<td>3</td>
<td>Australia</td>
<td>Total: ≥18 years 50 (16-74)/50 (28-70)</td>
<td>32 w</td>
<td>≥2 asthma exacerbations; require high-dose ICS in the previous years</td>
</tr>
<tr>
<td>Castro 2015; study 2</td>
<td>Res/Placebo</td>
<td>232/232</td>
<td>200/490</td>
<td>Yes</td>
<td>Multi</td>
<td>3</td>
<td>USA</td>
<td>12-75 years 48 (39.5-57)/48 (37-56.5)</td>
<td>52 w</td>
<td>≥1 asthma exacerbations; Require high-dose ICS in the previous years</td>
</tr>
<tr>
<td>Pavord 2012</td>
<td>Mep 75/Mep 250/Mep 750/Placebo</td>
<td>153/152/156/155</td>
<td>190/222/179/372</td>
<td>Yes</td>
<td>Multi</td>
<td>/</td>
<td>UK</td>
<td>Total: 12-74 years 50.2±10.8/49.4±11.6/46.4±11.3</td>
<td>52 w</td>
<td>≥2 asthma exacerbations</td>
</tr>
</tbody>
</table>

IV: intravenously; SC: subcutaneous injection; ICS: inhaled corticosteroids; LABA: long acting B agonist therapy; Ben 30 Q4w: Benralizumab 30 mg Q4w; Ben 30 Q8w: Benralizumab 30 mg Q8w; Mep 100 SC: Mepolizumab 100 SC; Mep 75 IV: Mepolizumab 75 IV; Res 3 mg / kg: Reslizumab 3 mg/kg.
A systemic review and network meta-analysis of randomized controlled trials

Exclusions contain: (1) review, retrospective research, case report, (2) insufficient data in the articles, (3) the dose of agents based on phase II or I.

Exclusions contain: (1) review, retrospective research, case report, (2) insufficient data in the articles, (3) the dose of agents based on phase II or I.

Outcome: annual exacerbation rate, (3) the dose of agents based on phase III randomized control trial, (4) only be published by English.

Statistical analysis

Data was pooled and odd ratios (OR) were used for the dichotomy outcome: the incidence of annual exacerbation of asthma. The total numbers of patients were multiplied by 10 to produce new total numbers, which were bigger than the annual rate of exacerbations multiplied by the number of asthma patients in each group of every study. Because in network metaanalysis of dichotomy, the total number must be bigger than every event. To make the new total number, every patient had 10 times the chance to have exacerbation in a year. All statistical analyses were carried out with Review Manager 5.2 (The Cochrane Collaboration) and Stata 15.1.

Results

This study included 10 RCTs with 5408 patients to determine what kind of regimen in IL-5 monoclonal antibodies based on the phase III RCTs could decrease the rate of annual exacerbations in patients with severe asthma. The quality of the article evaluations are as follows, and the studies included were well-prepared (Figures 2 and 3).

Network evidence of the comparisons for the different IL-5 monoclonal antibody agents are shown in Figure 4. Compared with placebo, all therapeutic regimens (benralizumab 30 mg q4w, benralizumab 30 mg q8w, mepolizumab 100 mg SC, mepolizumab 75 mg IV, and reslizumab 3 mg/kg) decreased the annual exacerbations with the OR (95% CI) value of 1.89 (95% CI 1.65-2.15).
CI 1.43, 2.51), 2.06 (95% CI 1.54-2.77), 2.17 (95% CI 1.64, 2.88), 2.09 (95% CI 1.51-2.89), 0.40 (95% CI 0.29-0.56), respectively. However, there was no significant difference between these therapeutic regimens (Figures 5, 6).

In network meta-analysis, heterogeneity was not compared in the study, but an inconsistency test was applied to find out whether the data of these studies could be mixed and calculated. The inconsistency test showed that the comparison could be performed by consistency (P>0.05) (Table 2). In the rank of network meta-analysis, it was found that reslizumab 3 mg/kg (57.3%) was the most effective therapeutic regimen to down the incidence of annual exacerbation in these patients with severe asthma, followed by mepolizumab 100 mg SC (14.9%), mepolizumab 75 mg IV (14.3%), benralizumab 30 mg q8w (10.8%), benralizumab 30 mg q4w (2.7%), and placebo (0.0%). The biggest probability means this therapeutic regimen has the biggest chance to be the best treatment (Table 3).

Discussion

Eosinophilic inflammation is evident in approximately half of patients with asthma and associated with increased disease severity, exacerbation frequency, symptom burden, as well as decreased lung function [15, 16]. IL-5, a critical cytokine for eosinophil development, activation, and survival, is present in increased concentrations in patients with asthma [17, 18]. Current asthma treatment guidelines recommend add-on IL-5 monoclonal antibody agents (mepolizumab, benralizumab, reslizumab) for patients with severe, uncontrolled, eosinophilic asthma [19]. A bronchoscopy study showed that treatment with IL-5 monoclonal antibody reduced airway mucosal eosinophil numbers by 55% in contrast to the 85% or more reduction in blood and sputum eosinophils [20]. IL-5 monoclonal antibody treatment had no effect on asthma symptoms, FE_{NO}l, or lung function, which suggests that symptoms, FE_{NO}l, and lung function have no connection with eosinophilic inflammation and will be improved by corticosteroid treatment through another mechanism [14].

Furthermore, compared with placebo, the IL-5 monoclonal antibody group had a lower annual rate of exacerbations. Ranking the regimens in the order of estimated probabilities of each treatment by using the network meta-analysis, showed that reslizumab 3 mg/kg was the best, followed by mepolizumab 100 mg SC, mepolizumab 75 mg IV, benralizumab 30 mg q8w, benralizumab 30 mg q4w, and placebo.

Mepolizumab is an IL-5 monoclonal antibody approved in Europe, Canada, USA, and other countries as an add-on therapy to patients aged 12 years or older with severe asthma and an eosinophilic phenotype [4]. Benralizumab is a humanized, afucosylated, monoclonal antibody against the alpha subunit of the IL-5 receptor, which can induce depletion of eosinophils through enhancing antibody-dependent cell-mediated cytotoxicity involving natural killer cells [8, 21, 22]. Reslizumab is a IgG4/k humanized monoclonal antibody composed of the complementarity-determining regions of a murine antibody to human IL-5 that has been grafted onto human frameworks. Reslizumab neutralizes circulating IL-5 by preventing it from
A systemic review and network meta-analysis of randomized controlled trials

Figure 5. Odd ratios of the comparisons for the IL-5 monoclonal antibody therapy.

Figure 6. Forest plots of the comparisons for the IL-5 monoclonal antibody therapy.
binding to eosinophils [23]. Although placebos or sham treatments, which leave airway inflammation untreated sometimes can control asthma symptoms [24, 25], they did not decrease annual exacerbations of asthma in this study. The previous two meta-analyses both showed that reslizumab may be more efficacious than other regimens [5, 6], which is similar to this study. However, the result presented here could be better applied in clinical practice.

In conclusion, IL-5 monoclonal antibody can decrease the annual rate of exacerbations in patients with severe asthma. Probably, the regimen of reslizumab 3 mg/kg is the optimal choice to treat these patients.

Address correspondence to: Wei Liao, Department of Intensive Care Unit, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China. Tel: 86-17728171396; Fax: 86-17728171396; E-mail: liao-wei1631@163.com

References


Table 2. Inconsistency test

<table>
<thead>
<tr>
<th></th>
<th>Direct Coef</th>
<th>Direct Std. Err</th>
<th>Indirect Coef</th>
<th>Indirect Std. Err</th>
<th>Differ Coef</th>
<th>Differ Std. Err</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>-0.879</td>
<td>0.151</td>
<td>-0.625</td>
<td>0.151</td>
<td>0.537</td>
<td>0.151</td>
<td>0.999</td>
</tr>
<tr>
<td>AE</td>
<td>0.636</td>
<td>0.144</td>
<td>0.366</td>
<td>0.144</td>
<td>0.271</td>
<td>0.144</td>
<td>0.999</td>
</tr>
<tr>
<td>BE</td>
<td>0.724</td>
<td>0.150</td>
<td>0.187</td>
<td>0.150</td>
<td>0.538</td>
<td>0.150</td>
<td>0.999</td>
</tr>
<tr>
<td>CD</td>
<td>0.127</td>
<td>0.269</td>
<td>-0.829</td>
<td>0.269</td>
<td>0.210</td>
<td>0.269</td>
<td>0.617</td>
</tr>
<tr>
<td>CE</td>
<td>0.764</td>
<td>0.158</td>
<td>1.009</td>
<td>0.158</td>
<td>-0.245</td>
<td>0.158</td>
<td>0.736</td>
</tr>
<tr>
<td>DE</td>
<td>0.759</td>
<td>0.187</td>
<td>0.474</td>
<td>0.187</td>
<td>0.285</td>
<td>0.187</td>
<td>0.653</td>
</tr>
<tr>
<td>EF</td>
<td>-0.919</td>
<td>0.170</td>
<td>-1.411</td>
<td>0.170</td>
<td>0.493</td>
<td>0.170</td>
<td>1.000</td>
</tr>
</tbody>
</table>

A: Benralizumab 30 mg Q4w; B: Benralizumab 30 mg Q8w; C: Mepolizumab 100 SC; D: Mepolizumab 75 IV; E: Placebo; F: Reslizumab 3 mg/kg.

Table 3. Estimated probabilities (%) of each treatment being the best

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Ben 30 Q4w</th>
<th>Ben 30 Q8w</th>
<th>Mep 100 SC</th>
<th>Mep 75 IV</th>
<th>Placebo</th>
<th>Res 3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.7</td>
<td>10.8</td>
<td>14.9</td>
<td>14.3</td>
<td>0.0</td>
<td>57.3</td>
</tr>
</tbody>
</table>
A systemic review and network meta-analysis of randomized controlled trials


